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Original Article

Effect of Fixed Dose Combinations Antituberculosis and Separate Formulations on Clinical Symptoms, Weight Gain, Adverse Effect and Plasma Concentration in Tuberculosis and HIV Coinfection Cases

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Abstract

Background : Fixed Dose Combination (FDC) was aimed to simplify TB therapy and facilitate physician and patient compliance. This study was aimed to evaluate the effect of FDC antituberculosis and separate formulations (SF) on clinical symptoms, weight gain, adverse effect and plasma concentration in TB/HIV cases during the intensive phase.
Methods : Prospective cohort study was conducted in public hospital, Jakarta. We recruited TB-HIV patients in May 2018-May 2019. Patients (over than 18 years old) diagnosed with TB-HIV who consumed either FDC or SF and had not received antiretroviral. A total of 36 subjects were included in this study, 20 subjects in FDC group and 16 subjects in SF group.
Results : There was not significant different between FDC and SF groups with an improvement of clinical symptoms (P = 0.70) and weight gain (P = 1.00). Gastrointestinal syndrome was 75% in FDC group; 62.5 % in SF group. Mean (±SD) of rifampicin, isoniazid, pyrazinamide plasma concentration after 2 weeks therapy in FDC group were 5.49 mg/L (±3.40 mg/L), 1.35 mg/L (±1.20 mg/L), 19.87 mg/L (±17.00 mg/L), respectively. Mean (±SD) of rifampicin, isoniazid, pyrazinamide plasma concentration in SF group were 6.42 mg/L (±4.80mg/L), 0.87 mg/L (±0.70 mg/L), 5.03 mg/L (±7.60 mg/L), respectively.
Conclusion : There was not significant different between FDC and SF groups on improvement of clinical symptoms and weight gain in intensive phase of therapy, the highest of adverse effects was gastrointestinal syndrome, and all subjects had normal reference ranges of rifampicin concentrations, and isoniazid and pyrazinamide below the normal range.

Keywords : coinfection TB-HIV, fixed dose combination, separated formulation.

INTRODUCTION

Tuberculosis (TB) is an infectious disease which causes second most death in the world after HIV. Indonesia was one of the 30 highest TB burden country in the world, including coinfection TB-HIV.[1,2] Moreover, strains of Mycobacterium tuberculosis that are resistant to standard anti-TB therapy are emerging in almost all areas reporting to the World Health Organization (WHO). The large number of tablets used in the treatment regimens of TB, long-term treatment and nonadherence to treatment regimen are believed to be major contributing factors to this public health problem.[3] Fixed Dose Combination (FDC) was aimed to simplify TB therapy and facilitate physician and patient compliance with treatment recommendations. A previous study from Indonesia showed that patient's adherence of the use of FDC was 72.7% compared to the use of SF was 65.5%, there was no difference of the adherence between FDC and SF groups (p = 0.601).[4] Al-Shaer *et al* mentioned that effectiveness was not different between FDC and SF as shown by mean time to sputum conversion (29.9±18.3 vs. 35.6±23 days, p=0.12). Similarly, there was no difference in the incidence of adverse events, except for visual one that was higher in SF group. Fixed-dose combination (FDC) formulations are currently recommended for the treatment of active tuberculosis (TB) Meanwhile, concerns were raised about adequate bioavailability of the component drugs, particularly rifampicin (RIF) due to its enhanced decomposition in the presence of isoniazid (INH). In addition, a systematic review showed that the use of FDC increased the risk of tuberculosis recurrence compared to the use of SF.[5] Therefore, we aimed to evaluate the effect of FDC antituberculosis and separate formulations (SF) on clinical symptoms, weight gain, adverse effect and plasma concentration in TB/HIV cases during the intensive phase.

METHODS

Prospective cohort study was conducted in public hospital, Sulianti Saroso infectious disease hospital, Jakarta. It recruited TB-HIV patients in May 2018–May 2019. The inclusion criteria were patients (over than 18 years old) diagnosed with TB-HIV who received anti-tuberculosis medications (either as FDC or SF) and had not received antiretroviral. The exclusion criteria were the patients had renal disease and or creatinine/urea and elevated of LFT (alanine aminotransferase [ALT] or aspartate aminotransferase [AST] values) including total bilirubin).

The subjects received first-line anti-TB medications (rifampicin, isoniazid, pyrazinamide, and ethambutol), either as FDC (rifampicin 150, isoniazid 75, pyrazinamide 400, and ethambutol 275 mg/tablet) or SF (rifampicin 450 or 600, isoniazid 300, pyrazinamide 500, and ethambutol 500 mg/tablet). The dose was calculated based on the patient's weight. We used the survival estimate formula to calculate the sample size. It was estimated that 23 evaluable patients in each group were included, considering an expected drop-out rate of 10%.

The effect was defined as an improvement of clinical symptoms (improved or deteriorated) and weight gain (no loss or weight loss) during the intensive phase (after 2 months therapy. We noted the clinical symptoms of subjects such as a persistent cough, chest pain, fatigue, loss of appetite, fever. Adverse effect was also defined as a clinical symptom and increased alanine transaminase (ALT) and aspartate transaminase (AST), assessed closely at each visit during the first and second weeks of the intensive phase therapy. Normal reference ranges were 0 to 45 IU/L; 0 to 35 IU/L for ALT and AST, respectively.

Plasma concentrations of FDC antituberculosis and SF were measured after 2 weeks therapy when the drug reached in steady-state. Blood samples were collected in the morning on EDTA tubes, 2 ± 2 hours after the subjects administered the FDC antituberculosis or SF. After centrifugation, plasma was transferred and stored at -80ºC until analysis. Plasma concentrations of FDC antituberculosis and SF were determined using liquid chromatography (LCMS/MS) method with UV detection at Pharma Metric laboratories, Jakarta.

Statistical analysis, categorical data were reported as frequency and percentages. Fisher test to compare categorical data between the two groups of comparison. We set the significance level of 0.05. All statistical analyses were performed using SPSS 19. The study protocol was approved by Sulianti Saroso Infectious Disease hospital ethics committee (No. 33/XXXVIII.10/VII/2018). All involved subjects signed informed consent forms.

RESULTS

A total of 36 subjects were included in this study (Table 1). Twenty subjects received FDC antituberculosis and 16 subjects received SF. Overall the subjects was on clinical stage-1 and 2 of HIV.

At baseline, positive smear pulmonary tuberculosis were 5 subjects (10% in FDC group and 18.8% in SF group), while they achieved sputum conversion at the end of the intensive phase (after 2 months therapy). In the FDC group, 2 (10%) subjects passed away, 3 (15%) subjects were discontinued therapy due to increased LFT and allergies, and 2 (10%) subjects were lost to follow up after 2 months therapy (intensive phase). Figure 1 showed the flow chart of recruited subjects.

There was not significant different between FDC and SF groups with improving clinical symptoms (P = 0.70) and weight gain (P = 1.00), Table 2 and 3. Table 4 showed all of subjects had normal range of AST/ALT

TABLE 1
Demographic and clinical characteristics of the study subjects

Variables	FDC group (N=20 subjects)	SF group (N=16 subjects)
Age (year)		
>35	7 (35)	7 (43.8%)
≤35	13 (65)	9 (56.3)
Sex		
Male	17 (85)	4 (75)
Female	3 (15)	4 (25)
Body Weight Index		
Low, n (%)	9 (45)	7 (44)
Normal, n (%)	11 (55)	9 (56)
Clinical stage of HIV		
I, n (%)	0	0
II, n (%)	0	0
III, n (%)	15 (75)	11 (68.75)
IV, n (%)	5 (25)	5 (31.25)
Opportunistic infection		
Yes	12 (60)	6 (37.5)
None	8 (40)	10 (62.5)
Smear-positive pulmonary tuberculosis at baseline		
Positive	2 (10)	3 (18.8)
Negative	18 (90)	13 (81.3)

results in the first week and second week of intensive phase. Gastrointestinal syndrome was 75% in FDC group; 62.5 % in SF group. Adverse effect of FDC and SF groups were presented in Figure 2.

Six (30%) subjects out of 20 subjects in FDC group and 9 (56,25%) subjects from 16 subjects in SF group, the plasma concentration at 2 hours (C2h) were measured after 2 weeks therapy. Only half of subjects was measured the plasma concentration at 2 hours due to financial reasons. Plasma concentration at 2 hours were described in Figure 3 and 4. Several studies stated that the lower concentration at 2 hours was defined as rifampicin (< 8 or < 4 mg/L); (isoniazid) < 3 or < 1.5 mg/L; and (pyrazinamide) < 35 or < 20 mg/L.6,7 In this study, mean (±SD) of rifampicin, isoniazid, pyrazinamide plasma concentration in FDC group were 5.49 mg/L (±3.40 mg/L), 1.35 mg/L (±1.20 mg/L), 19.87 mg/L (±17.00 mg/L), respectively. Mean (±SD) of rifampicin, isoniazid, pyrazinamide plasma concentration in SF group were 6.42 mg/L (±4.80mg/L), 0.87 mg/L (±0.70 mg/L), 5.03 mg/L (±7.60 mg/L), respectively.

DISCUSSIONS

This study evaluated an improvement of clinical symptoms and weight gain during the intensive phase. There was not significantly different between FDC and SF groups with improvement of clinical symptoms and weight gain. We assumed that the FDC product had a bioequivalence to the SF for each of its active components, including rifampicin.[8] Therefore strongly recommended that the product of FDC must be ensured that qualified active ingredients and excipients should be used.[8] However, our subjects were newly diagnosed TB/HIV and the use of FDC or SF antituberculosis in the first 2 months of treatment had not been relieved clinical symptoms and body weight. Meanwhile, in this study showed the proportion of deteriorated and weight loss

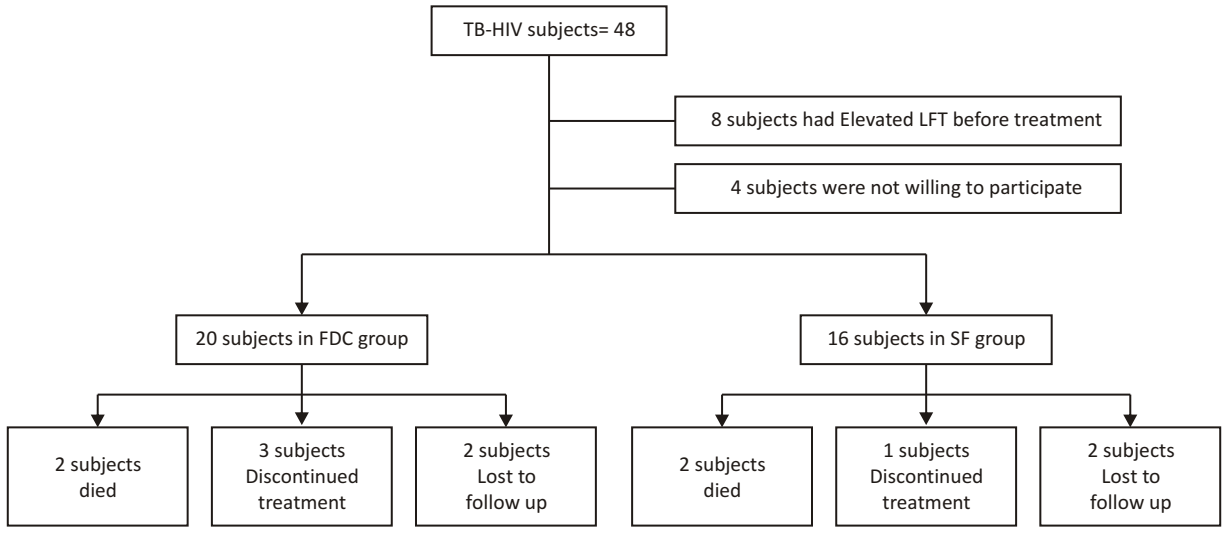

Figure 1. Flow diagram of subjects

TABLE 2
The proportion of subjects with an improvement of clinical symptoms during the intensive phase therapy

	Improved	Deteriorated	*P**	OR	CI 95%
FDC group	6 (30)	14 (70)	0.70	1.857	0.38 – 9.0
SF group	3 (18.8)	13 (81.3)			

*Fisher Exact

TABLE 3
The proportion of subjects with weight gain during the intensive phase therapy

	No loss (weight gain)	Weight loss	*P**	OR	CI 95%
FDC group	7 (35)	13 (65)	1.00	0.897	0.229 – 3.521
SF group	6 (46.2)	10 (62.5)			

*Fisher Exact

were higher. Weight loss is a major feature of TB/ HIV, which may affect both the severity and outcome of the disease. There was a hypothesis that the pathogens products can stimulate the production of proinflammatory mediators and cytokines. It stimulates the acute phase of the host response, which leads to anorexia.[9,10]

We did not evaluate acid-fast bacilli (AFB) sputum smear conversion as an outcome of the therapy due to the proportion of smear-negative was higher (over than 50%). Leandro *et al* showed that high prevalence of smear-negative (65.2%) among patients with TB in a tertiary care hospital of south of Brazil with high TB/HIV prevalence.[11] Previous studies demonstrated that TB/HIV patients are more likely to have smear-negative pulmonary tuberculosis, and this probability increases as immunosuppression increases.[12]

In this study, we evaluated adverse effect, particularly altered alanine transaminase (ALT) and aspartate transaminase (AST). We assessed closely at each visit during the first and second weeks in the intensive phase compared to the baseline ALT/AST. Baseline liver function are one of the risk factors for the development of drug induce hepatitis and these inform monitoring and management of these patients.[13] We did not find the elevation of ALT/AST of ≥ 3 during 2 weeks of intensive phase.[8] A small subject might contribute the results. However, hepatotoxicity attributed to FDC or SF

TABLE 4
Laboratory results (AST/ALT) at each visit during the first and second weeks of the intensive phase therapy

	FDC group n (%)	SF group n (%)
The first week of the intensive phase therapy (n= 36 subjects)		
Normal range of AST/ALT	20 (55)	16 (45)
Elevated of AST/ALT	0	0
The second weeks of the intensive phase therapy (n= 21 subjects)		
Normal range of AST/ALT	13 (62)	8 (38)
Elevated of AST/ALT	0	0

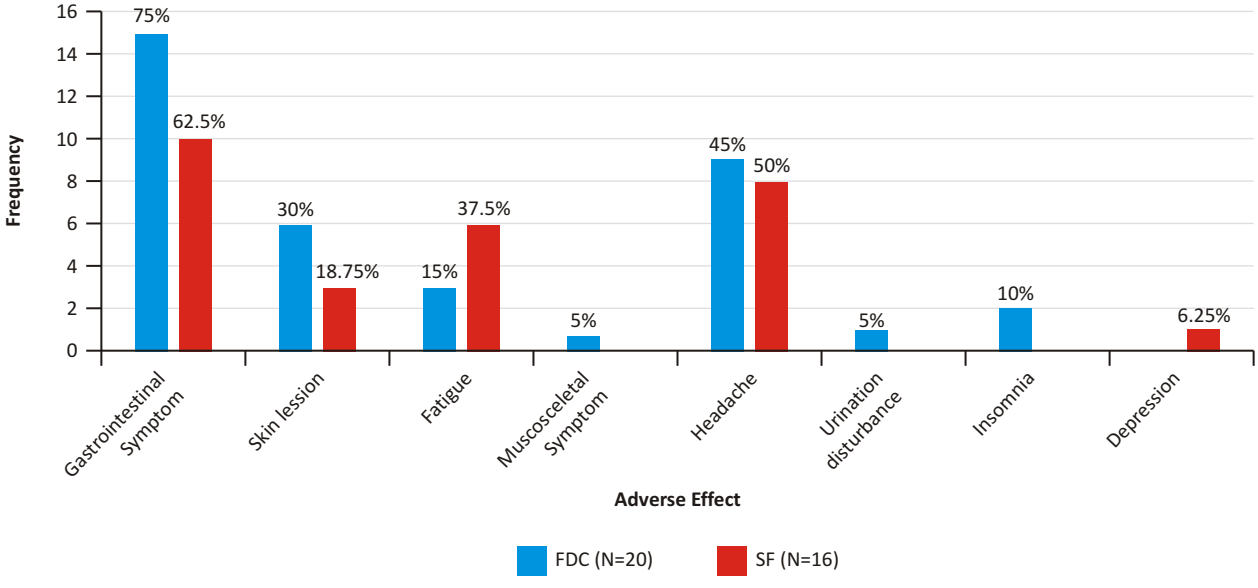

Figure 2. Adverse effect of FDC and SF groups

of antituberculosis has been reported in 5%–28% of people treated with antituberculosis drugs.[8,13] Another adverse effect such as gastrointestinal syndrome and headache are common in each group. Majdoub *et al* mentioned that urticaria, thrombocytopenia and leukopenia were common in patients treated with FDC due to significant difference in isoniazid and rifampicin in both groups.[14] Treatment regimen for TB is same in both HIV positive and HIV negative patients. However, HIV causes poor treatment outcomes of antituberculosis. Since this virus impairs immune system of the host therefore adverse effects due to antituberculosis are more common where there is an increase prevalence of HIV.[14]

Plasma concentrations are measured to evaluate the appropriate dose for subjects who are slow to respond to therapy, have multidrug resistance, are at risk of drug-drug interactions or have concomitant disease conditions that significantly complicate the clinical situation or failed to therapy.[15,16] This study showed that the subjects had normal reference ranges of rifampicin concentrations, and lower ranges isoniazid and pyrazinamide, in both groups. Sekai *et al*, showed that of 225 of pulmonary TB patients, low pyrazinamide plasma concentration was associated with poor treatment outcome than normal plasma concentration ($p < 0.01$).[17] However, we did not evaluate an association between low plasma antituberculosis concentrations and clinical outcome and adverse effect because of a small number of blood sampling, the blood sampling was collected from 7 subjects of FDC group and 10 subjects of SF groups. Moreover, we only collected one sample that we expected C2h of rifampicin, isoniazid and pyrazinamide might provide information of completed of drug absorption and was accepted as an estimated C-max.[18,19] Meanwhile, C2h

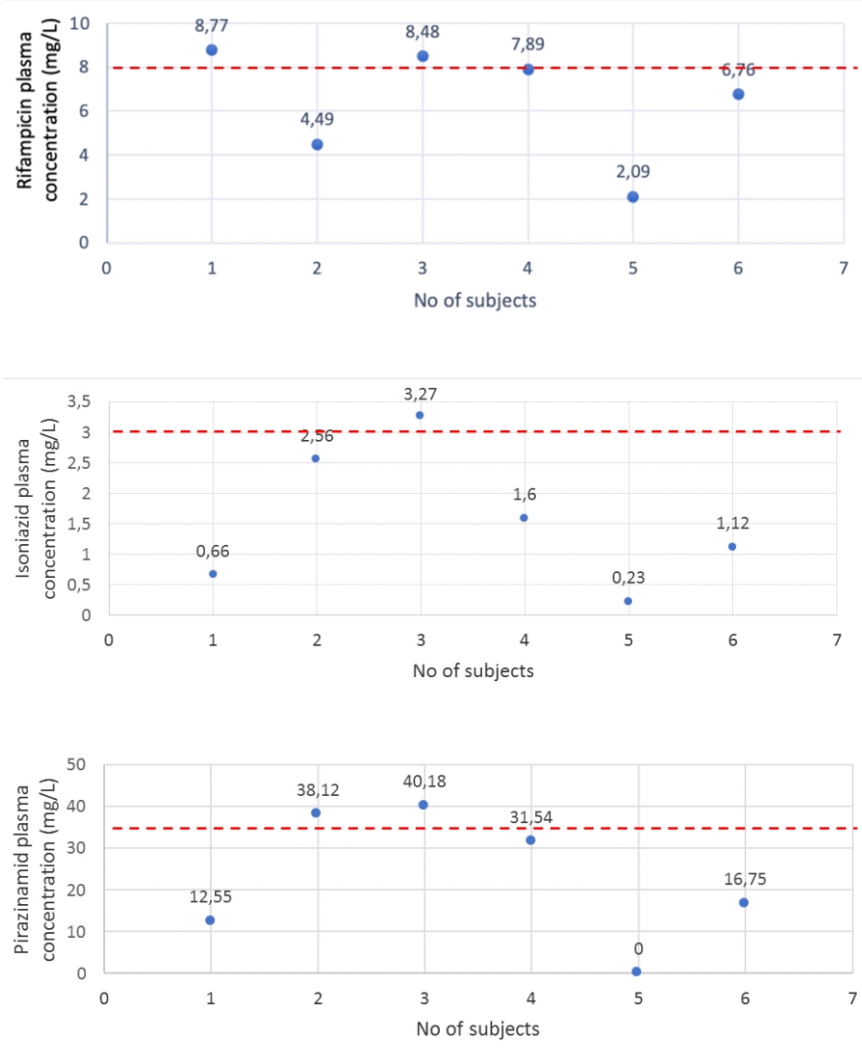

Figure 3. Mean plasma Rifampicin, Isoniazid, Pyrazinamide concentration (mg/L) in FDC group. The results of mean plasma Rifampicin, Isonizaid, Pyrazinamide concentration (mg/L) in each subject is showed by blue dots. The lower normal range in each drug is showed by horizontal a red dot line.

values cannot differentiate between the delayed absorption or malabsorption and a low peak concentration, ideally a second sample, often collected at 6-hour (C6h), can confirmed between delayed absorption and malabsorption.[16,18] From a prospective observational study at India mentioned that low C2h of isoniazid was 71%, rifampicin was 58%, ethambutol was 46%, pyrazinamide was 10% and both isoniazid and rifampicin were 45% of the patients. Therapy failure occurred more frequently in both isoniazid and rifampicin were below the normal ranges (p=0.013).[19] Um SW *et al* founded that among 69 enrolled TB patients had low C2h of antituberculosis drugs. The plasma concentrations of isoniazid, rifampicin and pyrazinamide were positively associated with dose per kilogram of body weight ($P < 0.05$), meanwhile isoniazid concentration was associated with acetyl isoniazid/isoniazid ratio. We know that metabolism of isoniazid, especially acetylation by liver N-acetyltransferase. Isoniazid can be acetylated to form acetyl isoniazid. Thus, the ratio of the plasma concentrations of acetyl isoniazid and isoniazid as a determinant of the type of slow or rapid acetylator.[16,20]

Previous studies demonstrated the important to compare of FDC and SF formulations. Abraham *et al* conducted a randomized clinical trial comparing FDC with SF which FDC appeared to be as effective and safe as SF, although the proportion of HIV patients was only 5%.[21] Wu JT *et al* mentioned that serum bilirubin concentrations at the peak level, at week 4, and at week 8 were significantly higher for FDC than SF (p=0.04, and 0.03, respectively).[2]

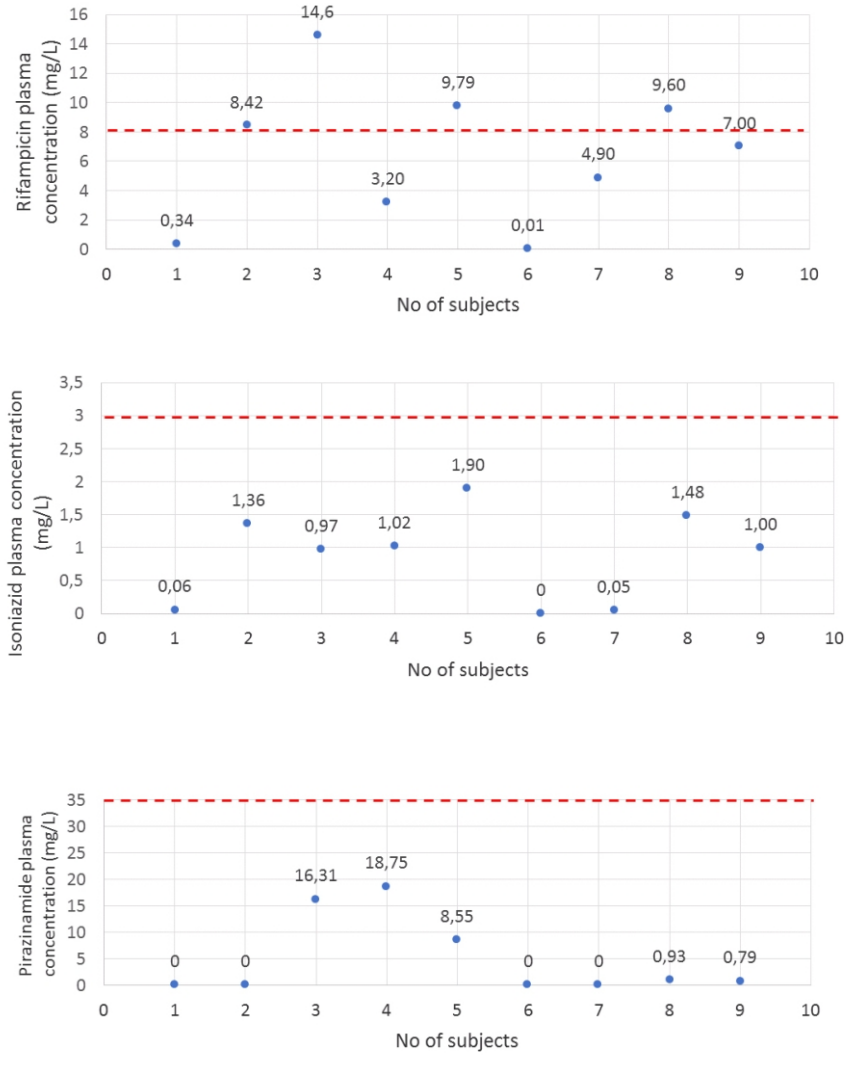

Figure 4. Mean plasma Rifampicin, Isoniazid, Pyrazinamide concentration in SF group. The results of mean plasma Rifampicin, Isonizaid, Pyrazinamide concentration (mg/L) in each subject is showed by blue dots. The lower normal range in each drug is showed by horizontal a red dot line.

Limitations of the study, to begin with our sample size was too small and cannot reach an estimated number in each group. Therefore, it might be difficult to find significant relationships from the data. In addition, we only collected one sample as C2h, which might miss the actual peak concentration. We suggest that further research with better designs are needed.

In conclusion, in intensive phase of therapy, there was not significant different between FDC and SF groups on improvement of clinical symptoms and weight gain, the highest of adverse effects was gastrointestinal syndrome, and all subjects had normal reference ranges of rifampicin concentrations, and isoniazid and pyrazinamide below the normal range. However, we should be directly observing patients with TB/HIV in intensive phase to complete their appropriate treatment.

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Conflict of Interest

We declare no conflict of interest in this study.

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